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| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
|--------------------|-------------|-----------------------|---------------------|

08/359,937 12/20/94 ILLUM

15M1/0927

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| L | EPC148C1 |
| EXAMINER | |
| KISHORE, G | |
| ART UNIT | PAPER NUMBER |

23

DATE MAILED: 1502

09/27/96

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

7-8-96

- ☒ Responsive to communication(s) filed on _____
- ☐ This action is FINAL.

- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 1-28 is/are pending in the application.
- Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-28 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claims _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of Reference Cited, PTO-892
- ☒ Information Disclosure Statement(s) 2
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

- SEE OFFICE ACTION ON THE FOLLOWING PAGES -

* U.S. GPO: 1996-409-290/40029

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DETAILED ACTION

Upon consideration, the finality of the previous action is withdrawn and the prosecution is reopened.

Claims included in the prosecution are 1-28.

Double Patenting

1. The obviousness type double patenting of claims 1-10 and 15-16 and the non-statutory double patenting of claims 11-14 (now extended to claims 17-28) are maintained in the absence of a terminal disclaimer.

Applicants' arguments that there is nothing in the disclosure of 5,204,108 to suggest instant sizes. This argument is not found to be persuasive. Claim 1 in said patent is a generic claim and does not recite any sizes and thus, it includes microspheres of instant sizes. With regard to applicants' arguments that in 108 there is no absorption enhancer, the examiner points out that instant claim 1 does not recite absorption enhancer and claim 7 recites the absorption enhancer, but no amounts. Claim 1 of 108 recites, 'substantially free of absorption enhancer' meaning that some enhancer could be present and thus, claim 1 of 108 encompasses even instant claim 7. Applicants' arguments that the method and system are not obvious over the claims in claims in the prior patent

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are not found to be persuasive since the this rejection is based on the full disclosure of the prior patent as set forth in the previous action.

Applicants' arguments have been fully considered, but are not found to be persuasive. The amendment to the independent claims will not overcome the rejection because what is introduced is an intended use and furthermore, applicants have not conclusively established that the cromoglycate administered by the same way in Illum does not enter circulation and thus provide a systemic effect.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1-6, 11-13 and 16 are rejected under 35 U.S.C. § 103 as being unpatentable over Illum (4,847,091)

Illum, as pointed out before teaches the same microspheres of instant for nasal inhalation (note the abstract, columns 1-3, examples and claims). Illum however, teaches the composition for only one drug, sodium cromoglycate. Although Illum's compositions are meant for the nasal tissue, it would be obvious to an artisan that systemic absorption of a drug when applied topically is dependent on the nature of the drug and thus, would

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be motivated to use the microspheres of Illum with other drugs, if the use of use of microspheres for systemic use is desired.

3. Claims 1-28 are rejected under 35 U.S.C. § 103 as being unpatentable over Illum (4,847,091) in view of Illum WO 88/09163 of record.

Illum (4,847,091) has been discussed above. As pointed out, Illum does not teach the use of microspheres for the administration of insulin and other polypeptide drugs. Illum also does not teach the inclusion of penetration enhancers.

Illum in WO teaches microspheres containing insulin and penetration enhancers (note the abstract, pages 7 -13 and claims).

The use of the microspheres of Illum 091 for the delivery of insulin and other polypeptide drugs for the systemic delivery would have been obvious to one of ordinary skill in the art with the expectation of obtaining similar absorption since Illum WO teach the use of the microspheres for such a delivery; the use of penetration enhancers would have been obvious to an artisan since according Illum WO, these enhance the absorption of insulin and other drugs.

4. Claims 1-28 for reasons of record, remain rejected under 35 U.S.C. § 103 as being unpatentable over Illum (1986).

Illum (1986) discloses albumin and starch microspheres which could be used to deliver drugs including peptides and proteins to the nasal mucosa. Illum further discloses that the microspheres could be modified by cross-linking (note the discussion section on

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page 207). According to Illum, such a system would ensure an increased time of contact between the delivery system and the mucosa by a process of bioadhesion with the possibility of additionally releasing the drug from the system in a sustained and controlled manner (note page 206). The important factors including the particle sizes are also disclosed by Illum (pages 206-207). Pump spray is disclosed on page 208.

Although Illum's teachings do not include the use of penetration enhancers, her disclosure includes the knowledge in the art of the use of such enhancers for nasal (mucosal) delivery of proteins (see 3rd paragraph, Introduction). Instant invention thus, is deemed to be an obvious extension of Illum.

5. Claims 1-28 for reasons of record, are rejected under 35 U.S.C. § 103 as being unpatentable over Illum (4,847,091) in view of Hanson et al or Salzman et al or vice versa.

Illum, 091 has been discussed above. What is lacking in these publications is the teaching of the use of the microspheres with polypeptide drugs such as insulin. What is also lacking is the teaching of the use of absorption enhancers.

Hansen et al disclose that biological response to nasal administration of calcitonin could be increased by the inclusion of various surfactants in the formulation (see the conclusion on page 241). Hansen et al's disclosure does not include the use of microspheres.

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Salzman et al disclose that intranasal administration of insulin in combination with a non-ionic detergent increases the absorption of insulin (note discussion on page 1081).

To use the microspheres of Illum 091 for the delivery of insulin and other polypeptide drugs would have been obvious to an artisan since Hansen and Salzman teach that insulin could be administered nasally for systemic effect and an artisan would expect at least similar absorption of insulin. To include penetration enhancers such as surfactants taught by Hansen et al or Salzman et al in the microspheres of Illum would have been obvious to one of ordinary skill in the art since such an inclusion would certainly increase the absorption of drugs from the mucosal membranes.

Alternately, to use the microspheres of starch or similar swellable and bioadhesive material as taught by Illum in the teachings of Hansen or Salzman would have been obvious to an artisan since such spheres adhere to the nasal tissue and allow the drug to be released in a sustained manner.

6. Claims 7-12, 14, 23-26 for reasons of record, are rejected under 35 U.S.C. § 103 as being unpatentable over Illum (1986) in view of Hanson et al or Salzman et al or vice versa.

Illum 1986 has been discussed before. What is lacking in Illum is the teachings of penetration enhancers. Hansen and Salzman have been discussed above.

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To include penetration enhancers such as surfactants taught by Hansen et al or Salzman et al in the microspheres of Illum would have been obvious to one of ordinary skill in the art since such an inclusion would certainly increase the absorption of drugs from the mucosal membranes.

Alternately, to use the microspheres of starch or similar swellable and bioadhesive material as taught by Illum in the teachings of Hansen or Salzman would have been obvious to an artisan since such spheres adhere to the nasal tissue and allow the drug to be released in a sustained manner.

Applicants' arguments have been fully considered, but are not found to be persuasive.

Applicants argue that Illum does not teach particles of sizes less than 20 micrometers and in fact Illum teaches away by suggesting the use of particles of sizes 40-60 microns. The examiner disagrees and points out that the sizes of 40-60 refers to the swelled sizes and instant claims do not recite swelled sizes of less than 10 microns. Illum's particles are intended to deliver therapeutic drugs such as insulin; insulin is known to be used of diabetes and it would thus, be obvious to an artisan that Illum teaches intranasal delivery intended of systemic effect. With regard to unexpected results argued by applicants, as pointed out above, the sizes of 40-60 in Illum are swelled sizes and for a proper comparison showing unexpected results, a comparison must be made with the unswelled sizes in Illum. Furthermore, significant improvement does not constitute unexpected

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results, but rather a routine experimentation by an artisan from Illum's suggestions regarding sizes on page 209, last four lines.

Applicants argue that nothing in Hanson or Salzman teaches or suggests the claimed formulation of microspheres of instant sizes. The examiner points out that these references were combined with the primary references to show the motivation for one of ordinary skill in the art to use surfactants; applicants provide no specific arguments regarding surfactant effect taught by these references.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to G. S. Kishore whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

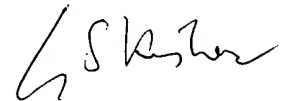
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K.Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-5408.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-2351.



Gollamudi S. Kishore, PhD
Primary Examiner
Group 1500

September 26, 1996